II. REMARKS

Formal Matters

Claims 1-8 and 10-22 are pending.

Claims 1-8, 10-14, 19, and 20 were examined and were rejected. Claims 15-18, 21, and 22 were withdrawn from consideration.

Applicant respectfully requests reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §103(a)

Claims 1-8, 10-14, 19, and 20 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Roses et al. (U.S. Patent No. 5,508,167; "Roses") in view of Huang et al. ((2001) *Proc. Natl. Acad. Sci. USA* 98:8838-8843; "Huang").

The Office Action stated:

1) Roses discloses a method for diagnosing Alzheimer's Disease (AD), comprising detecting apoE in a biological sample;
2) Roses teaches that the presence of an apoE4 indicates that the subject is afflicted with AD;
3) Roses teaches detecting apoE4 rather than carboxyl-terminal truncated apoE; and
4) Huang teaches that carboxyl-terminal truncated forms of apoE are found to be higher in patients with AD than in normal patients.

The Office Action concluded that it would have been obvious to modify the Roses method to diagnose a patient by detecting carboxyl-terminal truncated apoE. Applicant respectfully traverses the rejection.

The law regarding obviousness

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103(a), the Patent Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations.[1] In addition to demonstrating that all elements were known in the prior art, the Patent Office must also articulate a reason for

[1] M.P.E.P. § 2143(A).

combining the elements.[2] A generalized motivation to develop a method is not the kind of motivation required by the patent laws.[3]

In *KSR*, the Supreme Court reviewed the teaching-suggestion-motivation (TSM) test. While the Court warned against its rigid application,[4] the Court also found that the TSM test could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a).[5] The Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis."[6] Indeed, in *KSR*, the Court stated that the "Graham" factors[7] still control an obviousness inquiry. The Graham factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness.[8] Subsequently, the Federal Circuit reiterated the value of the TSM test, stating that a flexible TSM test remains the "primary guarantor against a non-statutory hindsight analysis."[9]

The Court in *KSR* repeatedly emphasized that an obviousness inquiry must take into account the predictability of the field:[10]

> the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

(emphasis added)

---

[2] *See, e.g., KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007) ("KSR") at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.,* 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*; and *Innogenetics, N.V. v. Abbott Laboratories,* 512 F.3d 1363, 1373, 85 USPQ2d 1641 (Fed. Cir. 2008).

[3] *Innogenetics, N.V. v. Abbott Laboratories,* 512 F.3d 1363, 1373, 85 USPQ2d 1641 (Fed. Cir. 2008).

[4] *KSR Int'l Co.,* at 1741.

[5] *Id. See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.

[6] *KSR Int'l Co.,* 127 S. Ct. at 1741.

[7] *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

[8] *KSR Int'l Co.,* 127 S. Ct. at 1734 (quoting *Graham, 383 U.S. at 17-18*).

[9] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.,* 520 F.3d 1358, 1364, 86 USPQ2d 1996 (Fed. Cir. 2008).

[10] *KSR Int'l Co.,* 127 S. Ct. at 1740 (citations omitted).

In *Eisai v. Reddy*,[11] Federal Circuit noted that the Supreme Court's analysis in *KSR* relies on several assumptions about the prior art landscape. These assumptions included: 1) a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions; 2) the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications; and 3) the record before the time of invention would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions. Such assumptions, while possibly relevant to mechanical devices such as were considered in *KSR*, may not be applicable to fields such as the chemical and biological arts.

When considering the Federal Circuit's application of the "obvious to try" standard to the adjustable gas pedal invention at issue, the Court stated:[12]

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

(emphasis added)

The Supreme Court in *KSR* stated that "a court *must* ask whether the improvement is more than predictable use of prior art elements according to their established functions."[13] The Court in *KSR* cited *Sakraida v. AG Pro*.[14] In *Sakraida v. AG Pro, Inc.*, the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious.[15]

Evidence that supports a finding of non-obviousness includes teaching away, unexpected results, skepticism of others in the field, copying, long-felt but unsolved need, and commercial success.[16] Such evidence must be considered before a conclusion of obviousness is reached.[17] Such evidence is not just a cumulative or

---

[11] *Eisai Co. Ltd. and Eisai, Inc. v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc.*, 2008 U.S. App. LEXIS 15399 (Fed. Cir. 2008).
[12] *KSR Int'l Co.,* 127 S. Ct. at 1742.
[13] *Id.* at 1740; (emphasis added).
[14] *Sakraida v. AG Pro, Inc.,* 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784 (1976).
[15] *Id.* at 282.
[16] *Graham,* 383 U.S. at 17 (1996).
[17] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

confirmatory part of the obviousness calculus, but constitutes independent evidence of non-obviousness,[18] or, as stated in *Hybritech*, consideration of such evidence is not merely "icing on the cake."[19]

The concept that teaching away is one of the indicia of non-obviousness is well established. In *United States v. Adams*[20] ("*U.S. v. Adams*"), the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: it contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.[21] The Court nevertheless rejected the assertion that Adams's battery was obvious. The Court relied upon the corollary principle that **when the prior art teaches away from combining certain known elements**, discovery of a successful means of combining them is more likely to be nonobvious.[22]

Comments regarding apolipoprotein E

Apolipoprotein E (apoE) is synthesized in the brain and by other organs such as the liver. At least 90% of serum apoE is synthesized by the liver. Studies have shown that **apoE synthesized by the liver does not enter the brain from the plasma**; and that **apoE synthesized in the brain does not enter the plasma**. See, e.g., Linton et al. (1991) *J. Clin. Invest.* 88:270. As such, those skilled in the art would not have expected apoE synthesized in the brain to be present in plasma.

As discussed below, Huang indicates that carboxyl terminal-truncated apoE is insoluble and was found intracellularly. Furthermore, production of carboxyl terminal-truncated apoE in the body has been shown to be **neuron specific**. Brecht et al. ((2004) *J. Neurosci.* 24:2527; "Brecht"). Brecht notes that apoE proteolysis, resulting in carboxyl-truncated apoE, is neuron specific. In view of studies showing that apoE synthesized in the brain does not enter the plasma, that carboxyl terminal-truncated apoE is insoluble, and in view of data showing that carboxyl terminal-truncated apoE is synthesized in the brain (and not in the liver), those skilled in the art would not expect carboxyl terminal-truncated apoE synthesized by the brain to enter the plasma or any other bodily fluid. As such, those skilled in the art would not expect, based on the disclosures of Huang and Roses, that one could detect carboxyl terminal-truncated apoE synthesized by the brain in a bodily fluid such as plasma.

The cited art neither discloses nor suggests a method of diagnosing AD, involving detecting a level of

[18] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.,* 520 F.3d 1358, 1365, 86 USPQ2d 1996 (Fed. Cir. 2008).
[19] *Hybritech,* 802 F.2d at 1380.
[20] *U.S. v. Adams,* 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966).
[21] *Id.* at 50, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293.
[22] *Id.* at 51, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293.

carboxyl-terminal truncated apoE in an aqueous biological sample.

Roses discusses methods of diagnosing AD. Roses discusses detecting apolipoprotein E4. Roses neither discloses nor suggests detecting carboxyl-terminal truncated apolipoprotein E (apoE).

Huang does not cure the deficiency of Roses. Huang does not disclose or suggest that carboxyl-terminal truncated apoE would be present in a biological sample other than brain, and thus could be detected in a diagnostic test for AD. Huang states that carboxyl-terminal truncated apoE is present in brains of AD patients. Huang, page 8839, column 2, first paragraph under "Results." Huang also states that carboxyl-terminal truncated apoE was detected in the lysates (not in the culture medium) of transfected Neuro-2a cells expressing apoE3 or apoE4. Huang, page 8840, column 1, first paragraph. Huang further states that carboxyl-terminal truncated apoE is present in intracellular inclusions. Huang, page 8840, column 2; and Figure 2. Thus, from reading Huang, one skilled in the art would not conclude that carboxyl-terminal truncated apoE would be present outside the brain, or in an aqueous biological sample that would normally be obtained from a living individual. As such, Roses, alone or in combination with Huang, cannot render instant claims 1-8, 10-14, 19, and 20 obvious.

The Office Action stated that "because Roses et al. disclose that bodily fluids such as blood and cerebrospinal fluid as well as tissues contain apoE that can be used in diagnosing Alzheimer's disease, the skilled artisan would be suggested to detect in non-tissue samples also the carboxyl-terminated apoE as disclosed by Huang et al. as a marker for Alzheimer's disease." Office Action, page 4.

However, it cannot be reasonably concluded, from a disclosure that apoE4 can be detected in bodily fluids such as blood, that carboxyl-terminal truncated apoE **produced by the brain** would also be present in an aqueous biological sample such as blood or serum.

First, as discussed above, apoE produced by the brain is generally not present in serum; instead, serum apoE is produced mainly by the liver. The Office Action appears to conclude that because Roses indicates that apoE4 can be detected in serum, that one could detect brain-produced apoE4 in serum. However, that is not what Roses discloses. Roses merely provides a method for determining whether a person has an apoE4 allele, by detecting apoE4 protein in the serum. As noted above, the vast majority of serum apoE is produced by the liver. The literature indicates that brain-produced apoE is not present in serum. As such, the assertion "because Roses et al. disclose that bodily fluids such as blood and cerebrospinal fluid as well as tissues contain apoE that can be used in diagnosing Alzheimer's disease, the skilled artisan would be suggested to detect in non-tissue samples also the carboxyl-terminated apoE as disclosed by Huang et al. as a marker for Alzheimer's disease" is without

merit.

Indeed, as shown in Figures 1a and 1b of Huang, carboxyl-terminal truncated apoE was found associated with neurofibrillary tangles (NFT), which are insoluble, intracellular formations and as such would not have been expected to be found in an aqueous biological sample such as serum or plasma.

Huang reports that carboxyl-terminal truncated apoE is found intracellularly in Neuro-2a cells, in NFT-like inclusions. Huang concludes that the "truncated apoE probably escapes the secretory or the endosomal-lysosomal internalization pathway, enters the cytosol, and interacts with p-tau and pNF-H." Huang, bridging sentence, pages 8840-8841. In view of such a disclosure, those skilled in the art would not conclude that carboxyl-terminal truncated is secreted, and therefore would not conclude that carboxyl-terminal truncated apoE would likely be found in bodily fluids such as serum.

Indeed, it was subsequently shown that production of carboxyl terminal-truncated apoE in the body is **neuron specific**. Brecht et al. ((2004) *J. Neurosci.* 24:2527; "Brecht"). Brecht notes that apoE proteolysis, resulting in carboxyl-truncated apoE, is neuron specific. In view of this observation, and in view of the observation in Huang that carboxyl-truncated apoE is in insoluble, intracellular formations, would not lead those skilled in the art to expect that carboxyl-truncated apoE would be found in the serum, plasma, or other aqueous biological sample.

There is no evidence in Roses or in Huang, or anywhere else in the literature, that carboxyl terminal-truncated apoE would be produced outside the brain, or that carboxyl-truncated apoE produced in the brain would be secreted, and thus could be found in fluids such as serum. As such, Roses, alone or in combination with Huang, does not render any of claims 1-8, 10-14, 19, and 20 obvious.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicant submits that the rejection of claims 1-8, 10-14, 19, and 20 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GLAD-281.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 17, 2008

By: /Paula A. Borden, Reg. No. 42,344/
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\GLAD (Gladstone)\281\Resp Final OA 7-24-08.doc